REMARKS

In accordance with the present amendments, claims 135, 137-138, 140-143 and 145-160 remain under consideration in this application. No claim has been allowed.

The Examiner has raised certain issues regarding the Information Disclosure Statement filed May 20, 2004 regarding certain of the cited references. Apparently, the even numbered pages were missing from some of the foreign patent documents and items numbered 54, 76 and 78 were not in proper citation format. Accordingly, a corrective Supplemental Information Disclosure Statement is being submitted with complete copies of the foreign references previously cited on page 1 of PCT Form 1449 of the May 20, 2004 Information Disclosure Statement and the Nguyen et al reference missing from the Information Disclosure Statement filed august 30, 2004 is also included. Complete citation data is not available for reference 78 (XP-002115938). However, 54, 76 and 78 have also been cited in greater detail. No new references are included in the Information Disclosure Statement.

Applicants gratefully acknowledge the withdrawal of certain rejections of record in the present Action, but believe that the rejections based on newly cited combinations in the present Action have actually raised new issues which have not previously been joined. Applicants believe they are entitled to a full and fair hearing on the new rejections and, because of this, the

finality of the rejection is believed to be premature. Applicants believe that the Examiner has not met the burden of MPEP § 70 6.07. The new grounds of rejection are not believed to have been necessitated by applicants' prior amendments. Therefore, reconsideration and withdrawal of the finality of the present Action is respectfully requested.

In any event, however, the following explanation of the difference between the present claims and the cited references are presented for consideration. Additional support for applicants' position that the present claims are patentable over the cited combination follows.

The rejection of claims 135, 137, 138, 140-143 and 145-159 under 35 USC § 103(a) as being unpatentable over Brinster and Zimmermann (1994, PNAS, USA, 91:11298-11302) in view of newly-cited Vogel and Sarver (1995, Clinical Microbiology Reviews, 8:406-410) is respectfully traversed.

It is noted with respect to Brinster and Zimmermann that the Examiner cites a particular passage as evidence of the positive teaching of that reference, namely page 11301, second column, last paragraph. Applicants believe the reference is far from the positive teaching represented in the current Office Action. In this regard, some analysis of the Brinster and Zimmermann disclosure is believed warranted and, in the above-cited paragraph, the following is stated in the second sentence:

"If spermatogonia can be cultured and manipulated --

eg, via targeted homologous recombination of DNA sequences -- and individual modified clones of cells can be selected in a manner similar to embryonic stem cells (18, 19), then these cells could be used to create mice with germ line modifications" (emphases added).

With respect to the above passage, the Examiner is asked to note the use of the words "if", "then", and "could" which suggests that there is doubt in the authors' minds that this is a possibility that will work in any event. In fact, it was perceived at the time that the culture of male germ cells was difficult and that it was difficult to retain the cells' integrity and male germ cell character in culture.

Secondly, even if those skilled persons were to consider attempting to manipulate spermatogonia, they are specifically taught to do so "*via targeted homologous recombination of DNA sequences*". As is clear from Capecchi (1989, Trends in Genetics, 5:70-76; also cited by the Examiner), this is totally different from the use of integrating viruses (see Figure 5 of Capecchi on page 75 which highlights the differences in these approaches). In fact, the whole thrust of Capecchi is to allow gene targeting in embryonic stem (FS) cells which requires homologous recombination between DNA sequences residing in the chromosome and newly introduced DNA sequences (see Abstract on page 70 of Capecchi).

Thus, Brinster and Zimmermann, to the extent that it may be relevant, suggests trying homologous recombination and not the use of viral vectors which integrate in the genome. Furthermore, Brinster and Zimmermann discloses only *targeted homologous recombination:* integration of virus or virus-derived DNA is not targeted.

Thirdly, Brinster and Zimmermann gives two specific references (References 18 and 19) for the genetic modification contemplated. Reference 18 is Capecchi (above) which is directed at gene targeting. Reference 19, Smithies (1993) Trends in Genetics 9, 112-116, (abstract cited and included as Appendix A attached) is a review of animal models of human genetic disease and, as can be seen from its abstract, relates to gene targeting in ES cells and not the use of viruses in male germ cells.

It is believed that combining Brinster and Zimmermann in view of Vogel and Sarver does not add information that is more relevant to the patentability of the present claims. The Vogel and Sarver reference is directed to nucleic acid vaccines which has nothing to do with making transgenic animals. The reference is believed to deal with subject matter far enough afield that it would not be consulted by one skilled in the art with respect to the subject matter of the present claims and therefore, for this reason alone, the combination should not stand.

Moreover, with respect to fundamental differences between what is taught or suggested by Vogel and Sarver and any

motivation to use viral DNA or viral derived DNA, it is noted at the outset that nucleic acid vaccines work by the nucleic acid being able to express a polypeptide which acts as an antigen in an immune response. There is no requirement for the nucleic acid to be in a viral vector or for it to integrate into the chromosome in order to do this.

This is plain from the section entitled "Nucleic Acid Vaccine Development" on page 406 in which it is made clear that (1) DNA expression vectors in cationic lipid vesicles can be used or (2) naked plasmid DNA vectors. The work of Davis et al (Reference 5 on page 407, column 1) demonstrates that, at least in some tissues (eg regenerating muscle), recombinant plasmid and adenoviral vectors (non-integrating) are superior to retroviral vectors (integrating).

Given the above, one can only conclude that there is nothing whatsoever in Vogel and Sarver which gives any guidance as to which, if any, of these systems would be applicable to the genetic manipulation of male germ cells. This is not surprising since Vogel and Sarver is in such an unrelated field.

Furthermore, it appears that the present rejections represent an analysis based on an impermissible hindsight reconstruction of the invention. The Examiner has attempted to reconstruct the claimed invention not from a position of what the skilled person would do in modifying the teachings of Brinster and Zimmermann (which, if anything, is to attempt to use

homologous recombination on spermatogonial cells), but impermissibly using knowledge gleened from the claimed invention and casting around to try to find a paper which "fills in the gap" of Brinster and Zimmermann. Vogel and Sarver cannot do this since, as discussed, it is in a different field (vaccines) and so would not be considered by the skilled person in any event. Furthermore, Vogel and Sarver in any event discloses a range of ways in which one could potentially genetically manipulate cells without suggesting any particular one.

It should be remembered that the authors of Kim et al (which has been discussed previously), who presumably were aware of a desire that any genetic manipulation of the cells was carried to the next generation, used a liposome-mediated gene delivery approach. It is noteworthy that Kim et al was published in 1997, i.e., immediately before the claimed priority date and some 2-3 years later than Brinster and Zimmermann, thus indicating again that the use of integrating viral vectors was not obvious to the skilled person.

For the above and other reasons, it is believed that the present rejection of claims 135, 137, 138, 140-143 and 145-159 cannot properly be sustained and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Claim 135 is believed to be allowable based on the above discussion and, for this reason, claim 160, which depends from 135, should also be in condition for allowance.

It is noted, however, that claim 160 has been made the subject of a separate rejection under 35 USC § 103(a) in view of the above two cited references and in further view of Wivel and Walters (1993, Science, 262:533-538), also newly cited. Applicants also respectfully traverse this rejection.

Claim 160, by virtue of its dependency from claim 135, clearly relates to "non-human vertebrate species". Wivel and Walters, on the other hand, is directed to a discussion of potentially human genetic intervention. Thus, that newly cited reference relates only to the generality of germ-line gene modification in the context of disease prevention in humans.

There is no disclosure in Wivel and Walters of male germ cell modification and, in fact, page 533, column 3 about half-way down notes:

> "It must be acknowledged, however, that at present most of the experimental work involves DNA transfer into one of the pronuclei of the zygote, the delivery of DNA into a four or eight-cell embryo by a vector, or the use of embryonic stem cells".

Given the above, the applicants believe that the further combination of Wivel and Walters with Brinster and Zimmermann and Vogel and Sarver would not suggest the invention claimed in claim 160.

In view of the above explanatory discussion, entry of this paper, withdrawal of the present rejections and allowance of the

claims is respectfully requested. In the alternative, if all claims are not found allowable, the withdrawal of a finality of the present Action, pending full development of the issues, is respectfully requested.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment Under 37 CFR 1.116 to a paper dated on July 26, 2005, in application Serial No. 10/008,385, filed on November 12, 2001, of Carol W. Readhead et al, entitled "TRANSFECTION, STORAGE AND TRANSFER OF MALE GERM CELLS FOR GENERATION OF TRANSGENIC SPECIES & GENETIC THERAPIES", and a transmittal letter are being sent by facsimile transmission to: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on September 16, 2005.

Barbara L. Davis
On behalf of C. G. Mersereau

Date of Signature: September 16, 2005

APPENDIX A

1: Trends Genet. 1993 Apr;9(4):112-6.

Animal models of human genetic diseases.

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Gene targeting in cultured embryonic stem cells permits the generation of mice with a desired alteration in a chosen target gene. Application of this procedure to create mouse models of human diseases is revealing the innate complexity of diseases normally ascribed to single gene defects. Modeling human diseases that are known to be multigenic in origin and are markedly influenced by environmental factors is potentially even more revealing.

Publication Types:
- Review
- Review, Tutorial

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